11. EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

Intent to Treat Efficacy Data Sets

All patients who were randomized, received treatment with study device, regardless of study completion, and had at least one post-treatment efficacy evaluation were included in the ITT population. Treatment assigned to the donor site at the time of randomization was used for all listings, tables, analyses and graphs presented in this report.

All 82 patients enrolled in the study were included in the ITT population.

Table 11.1.1: ITT, Per Protocol, and Safety Populations

Intent-to-Treat	82 (100%)
Per Protocol	74 (90.2%)
Safety	82 (100%)

Source: Section 14, Table C1

Per Protocol Efficacy Data Sets

These data sets were a subgroup of the ITT efficacy data sets, which excluded patients with major protocol violations. Eligibility criteria for this population were established at a Validity Meeting on 13 November 2000, prior to unblinding the study and consisted of the following:

- Exclusion for incomplete planimetry data. Incomplete planimetry was defined as not enough planimetry data to determine if the donor site was healed by the Day 28 study visit.
- Exclusion for violation of inclusion or exclusion criteria or any other major protocol violation.

Patients were not excluded from the PP population for systemic corticosteriod use before or during the study. The rationale for this decision was that the matched pairs design of the study would render both treatment sites equally vulnerable to any steroid effects on wound healing.

Of 82 randomized patients, eight patients were excluded from the PP population due to major protocol violations (See Section 10.2).

11.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Table 11.2.1 summarizes the demographic characteristics of the 82 enrolled subjects.

The population randomized to treatment was composed of 63 males (76.8%) and 19 (23.2%) females. Mean age of all patients was 31.7 years (range: 1 to 88 years). The population was 53.7% Caucasian, 24.4% African-American, 15.9% Hispanic, 2.4% Asian/Pacific Islander and 3.7% other.

Table 11.2.1: Demographics of All Randomized Subjects

Sex		
Male	n (%)	63 (76.8)
Female	n (%)	19 (23.2)
Race		
Caucasian	n (%)	44 (53.7)
African American	n (%)	20 (24.4)
Hispanic	n (%)	13 (15.9)
Asian/Pacific Islander	n (%)	2 (2.4)
Other	n (%)	3 (3.7)
Age (years) (n=82)	Mean (SD)	31.7 (±21.3)
Height (inches) (n=80)	Mean (SD)	61.2 (±13.7)
Weight (pounds) (n=82)	Mean (SD)	148.8 (±70.6)

Source: Section 14, Table C6

Over 80% of the study population had medical histories relating to dermatologic, endocrine/metabolic or neurologic disorders. Skin was the only organ system that yielded abnormal findings on physical examination in the majority of patients. (Section 14, Tables C10 and C11 provide baseline summary data for medical history and screening physical exam, respectively. Appendix 16.10, Listings 6 and 7 provide medical history and physical exam data, respectively, for individual patients).

With regard to the severity of injuries at baseline, Table 11.2.2 presents descriptive statistics for protocol-specified injury severity scales, daily caloric requirements, and percentage of total body surface area (TBSA) burned of randomized subjects.

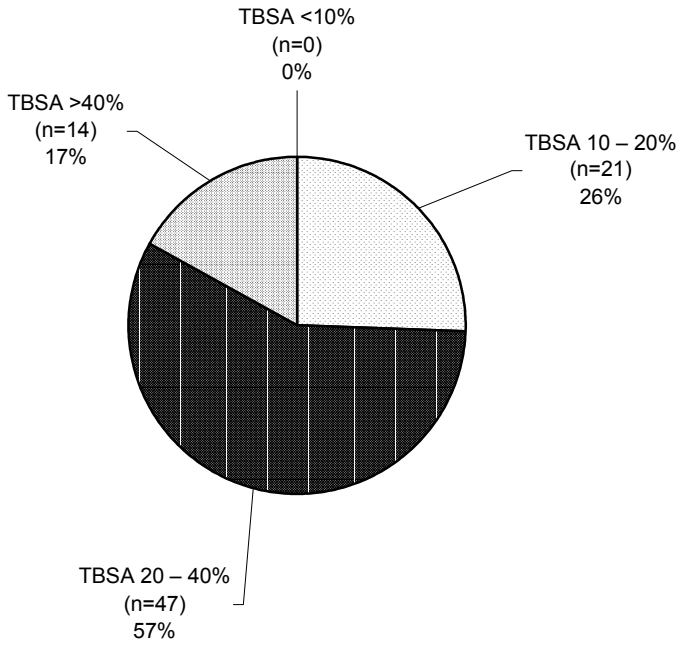
Table 11.2.2: Baseline Characteristics of Injury Severity

Daily caloric requirement	N	82
	Mean (SD)	2383.9 (756.56)
	Median	2379.5
	Range	568-4400
Injury Severity Score (ISS) (subjects ≥15 years of age)	N	50
	Mean (SD)	14.6 (8.12)
	Median	11.0
	Range	4-50
Pediatric Trauma Score (PTS) (subjects <15 years of age)	N	18
	Mean (SD)	8.9 (1.28)
	Median	8.5
	Range	7-11
Pediatric Glasgow Coma Score (subjects <15 years of age)	N	19
	Mean (SD)	14.8 (0.92)
	Median	15.0
	Range	11-15
Percentage of TBSA Burned	<10%	0 (0.0%)
	10 – 20%	21 (26%)
	20 – 40%	47 (57%)
	>40%	14 (17%)
	Total	82 (100%)

Source: Section 14, Tables C7 and P10, Section 16.10 Listing 6

The mean ISS and the mean PTS were 14.6 and 8.9, respectively, and the mean Pediatric Glasgow Coma Score was 14.8. A mean caloric intake (2384 calories) indicates that the majority of patients were in a catabolic state as a result of the severity of their injury. None of the randomized subjects had less than 10% TBSA burned and 74% of subjects had greater than 20% TBSA burned, as indicated in Figure 11.2.3.

Figure 11.2.3: Extent of Burn Injuries



TBSA = Total Body Surface Area
Source: Section 14, Table P10

Routine laboratory data obtained at the screening visit are summarized, descriptively, in Section 14, Table C12 and listed in Appendix 16.10, Listing 36. A total of 55 subjects (82%) had anemia and 35 subjects (52%) had elevated white cell counts. Over one third of the subjects (27/76, 36%) had elevated glucose levels. Additionally, decreased mean and median albumin levels (2.0 and 2.1g/dL, respectively, lower limit of normal is 3.5 g/dL) indicate that the population, as a whole, was malnourished. The screening laboratory results substantiate a patient population that was seriously ill.

Results of baseline medical histories, injury severity ratings, burned surface area, caloric intake, hematologic and chemistry parameters describe a population that was severely burned, malnourished, and debilitated. These factors indicate a possible predisposition to longer healing times in the studied population.

The treatment groups were well balanced with respect to donor site characteristics. Mean surface areas for the CCS and Biobrane L donor sites were 94.4 and 94.3 cm^2, respectively (p = 0.97). The mean autograft thickness of both the CCS and Biobrane L donor sites was 0.0116 inches (Section 14, Table C9 and Appendix 6.10, Listing 18).

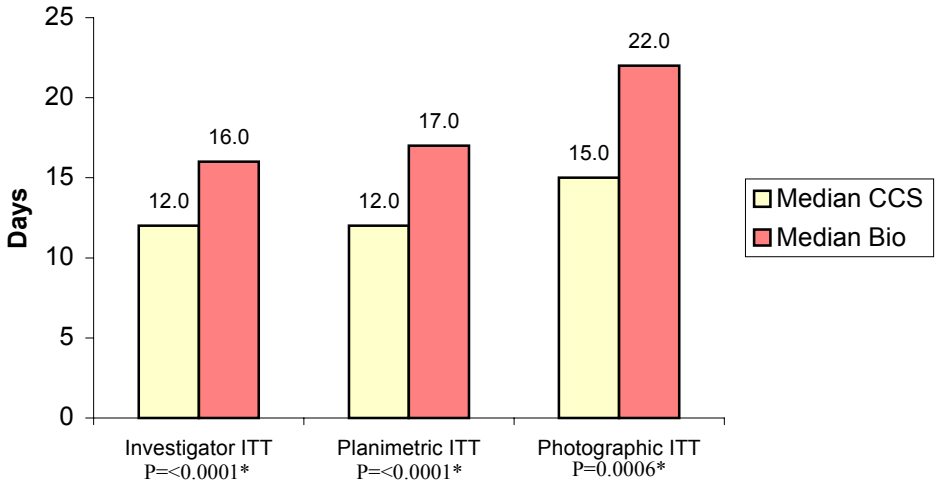
11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Not applicable

11.4 EFFICACY RESULTS

There was a clinically meaningful and statistically significant shorter time to 100% wound closure with CCS when compared to Biobrane-L. This finding was observed in three different methods of assessments (i.e., planimetric, photographic, and investigator assessments); evaluated with three different statistical metrics (i.e., mean, median, and Kaplan-Meier estimates) in two protocol specified populations (i.e., Intent-to-Treat and Per Protocol). The difference was also clinically and statistically significant in all subgroups where the patient numbers were greater than five (i.e., age, race, gender, percentage of total body surface area burned, and donor skin size).

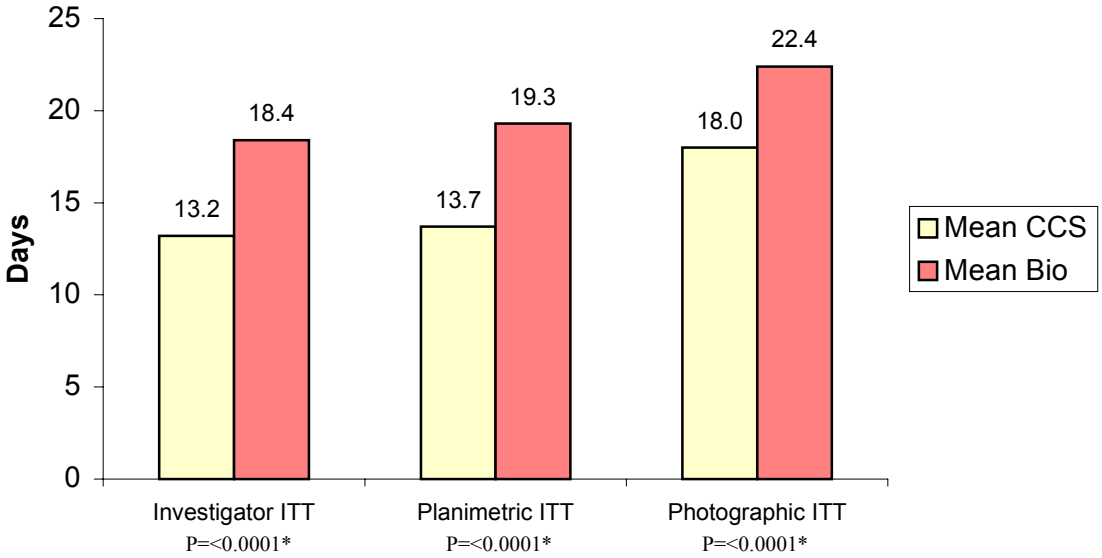
Figure 11.4.1: Median Days to 100% Wound Closure
ITT Population
(Investigator, Planimetric, Photographic Assessments)



*Log-Rank test of the difference between treatment healing times, stratified by patient
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Tables E18.3, E1.3, E9.3

In this section we present these findings in detail. We will use Kaplan-Meier curves to depict the percentage of donor sites completely healed over time. We also present the rate of wound closure as well as the percentage of donor sites completely healed by day 32 using the three methods of assessment and the two different populations. Additionally, using planimetry data we will demonstrate that in the first 16 days after donor skin harvest (i.e., 50% of the duration to day 32) the rate of wound closure at CCS-treated donor sites was nearly 70% faster of that of the Biobrane-L-treated sites.

Figure 11.4.2: Mean Days to 100% Wound Closure
ITT Population
(Investigator, Planimetric, Photographic Assessments)



*paired t-test
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Tables E18.1, E1.1, E9.1

11.4.1 PRIMARY EFFICACY PARAMETER

Primary efficacy data (i.e., time to 100% wound closure) are presented in Table 11.4.3 for the ITT and PP populations and the three methods of assessment.

Table 11.4.3: Median and Mean Days to 100% Wound Closure

	Median Days to Wound Closure*				Mean (SD) Days to Wound Closure			
	Source	CCS	BIO	p-value**	Source	CCS	BIO	p-value+
Investigator ITT	E18.3	12.0	16.0	<0.0001	E18.1	13.2(4.87)	18.4(7.86)	<0.0001
Investigator PP	E19.3	12.0	16.0	<0.0001	E19.1	12.9(4.16)	17.9(7.51)	<0.0001
Planimetric ITT	E1.3	12.0	17.0	<0.0001	E1.1	13.7(5.83)	19.3(8.37)	<0.0001
Planimetric PP	E2.3	12.0	16.0	<0.0001	E2.1	13.4(5.14)	18.7(8.02)	<0.0001
Photographic ITT	E9.3	15.0	22.0	0.0006	E9.1	18.0(7.12)	22.4(8.48)	<0.0001
Photographic PP	E10.3	15.0	21.0	0.0009	E10.1	17.8(6.64)	22.1(8.25)	<0.0001

*Kaplan-Meier estimates of the median days to 100% wound closure +Paired t-test
**Log-Rank test of the difference between median healing times
Source: Section 14, tables specified above

ITT Population

As specified in the protocol, the primary endpoint is 100% wound closure using photographic assessments. Figures 11.4.1 and 11.4.2 depict the median and mean times, respectively, to 100% wound closure across all three methods of assessment, photographic, planimetric, and investigator. For the ITT population and median days to healing using photographic assessment, CCS treated sites healed seven days faster than the Biobrane-L treated sites (15 days vs. 22 days, respectively); this was statistically significant with p-value=0.0006. For mean days to healing by photographic assessment, CCS treated sites in the ITT population healed four days faster than the Biobrane-L treated sites (18 days vs. 22 days, respectively), also statistically significant (p<0.0001).

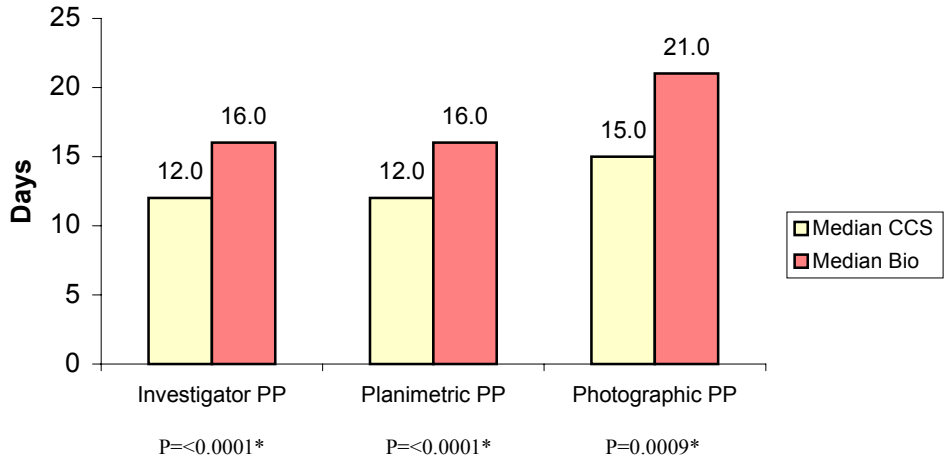
Results of ITT planimetric assessments support those obtained by photography (i.e., median and mean days to healing for CCS were 12 and 14 days, respectively, while those of Biobrane-L were 17 and 19 days, respectively). These differences reflect a five-day shorter time to healing with CCS and are statistically significant (p=<0.0001).

Results of the ITT investigator assessment also support those obtained by photography; i.e., median and mean days to healing for CCS were 12 and 13 days, respectively, while those of Biobrane-L were 16 and 18 days, respectively, reflecting a four- to five-day shorter time to healing with CCS that is statistically significant (p<0.0001).

Per Protocol Population

Figure 11.4.3 depicts the photographic, planimetric and investigator assessments of time to 100% wound closure for the PP population. Results obtained with this population closely resemble those of the ITT population with statistically significant differences in time to wound closure for all three assessment methods.

Figure 11.4.3: Median Days to 100% Wound Closure
Per Protocol Population
(Investigator, Planimetric, Photographic Assessments)



*Log-Rank test of the difference between treatment healing times, stratified by patient
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Tables E19.3, E2.3, E10.3

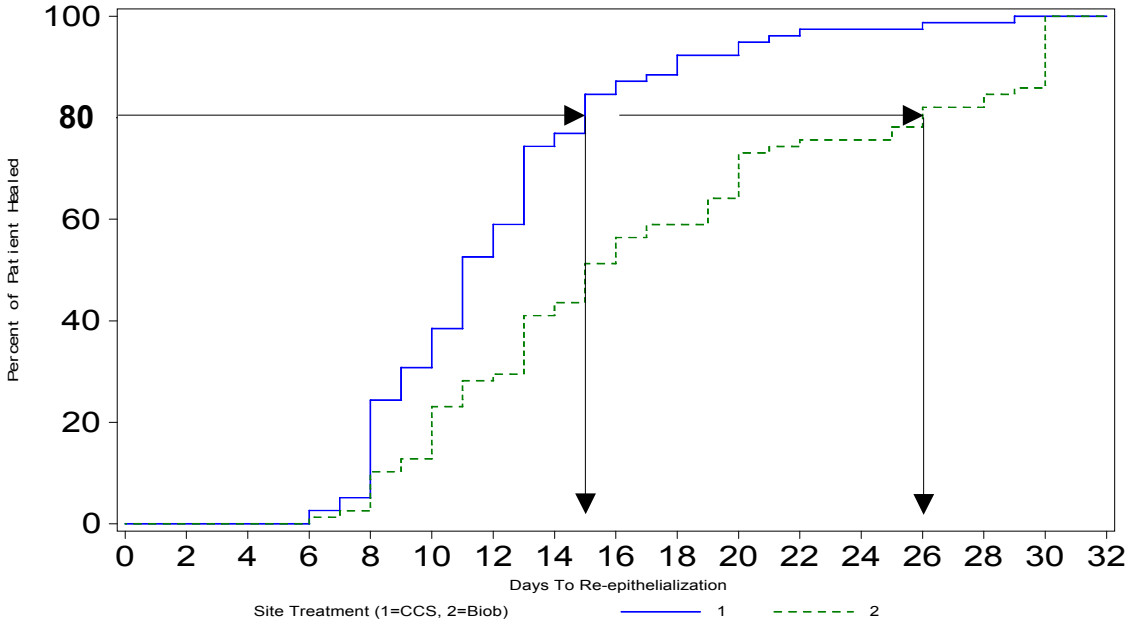
For the photographic assessment, CCS treated sites healed six days faster than the Biobrane-L treated sites (15 days vs. 21 days, respectively), a statistically significant difference ($p = 0.0009$). Mean time to healing was 18 vs. 22 days, respectively ($p<0.0001$).

Results of planimetric and investigator assessments were similar to the photographic assessment with CCS treated sites requiring only 12 days to wound closure (median time) while Biobrane-L treated sites required 16 days, again, reflecting a statistically significant difference between the two treatments ($p<0.0001$) for both assessments. Mean time to healing by planimetry was 13 vs. 19 days, respectively ($p<0.0001$). Mean time to healing according to investigators assessment was 13 vs. 18 days, respectively ($p<0.0001$).

Kaplan-Meier Presentation

To depict the time to wound closure in more detail, the Kaplan-Meier (K-M) curve waas employed. Figure 11.4.4 is the K-M curve for time to 100% wound closure based on investigator assessments for the ITT population. The horizontal axis presents days and the vertical axis presents percentage of patients healed. To explain this graph, we draw an arrow at 80% on the vertical axes (percent of patients healed) and demonstrated its associated time to healing on the horizontal axes for CCS (15 days) and for Biobrane-L (26 days).

Figure 11.4.4: Investigator Assessment of Time to 100% Wound Closure ITT, Kaplan-Meier



Figures 11.4.5 and 11.4.6 depict K-M curves for the planimetric and photographic assessments, respectively, in the ITT population. Results from all three methods of assessment indicate the superior healing power of CCS as compared to Biobrane-L in terms of time of healing. By planimetric assessment, 80% of all CCS donor sites achieved complete closure by day 15 as compared to day 28 for complete closure of 80% of the Biobrane-L sites. Per photographic assessment, 80% of all CCS donor sites

achieved complete closure by day 22 as compared to day 29 for the Biobrane-L donor sites.

Figure 11.4.5: Planimetric Assessment of Time to 100% Wound Closure ITT, Kaplan-Meier

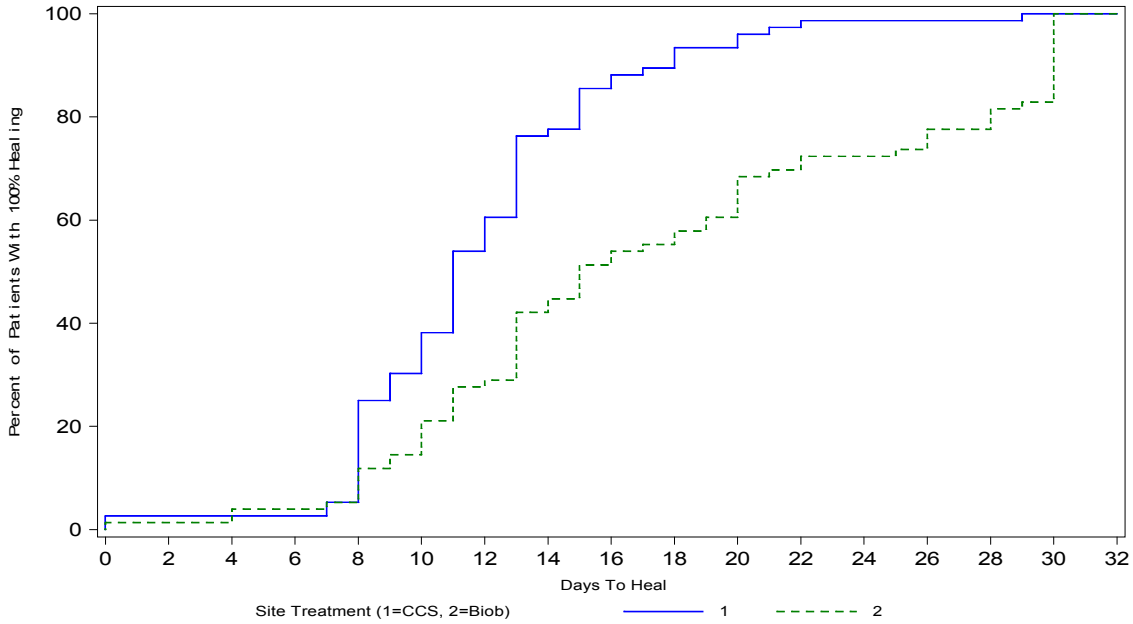
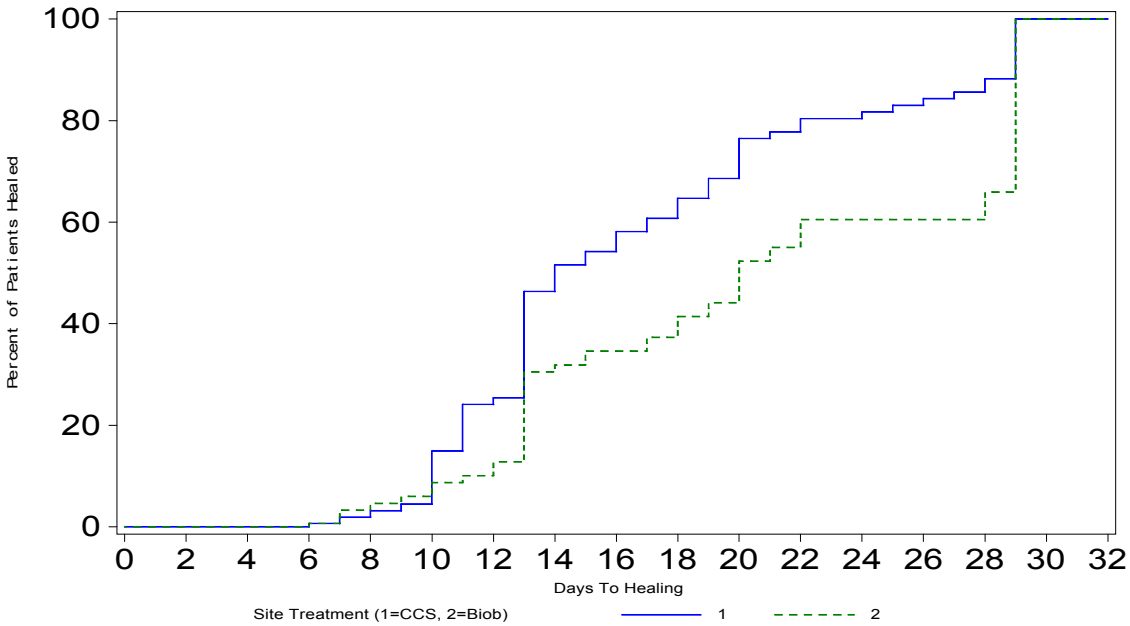


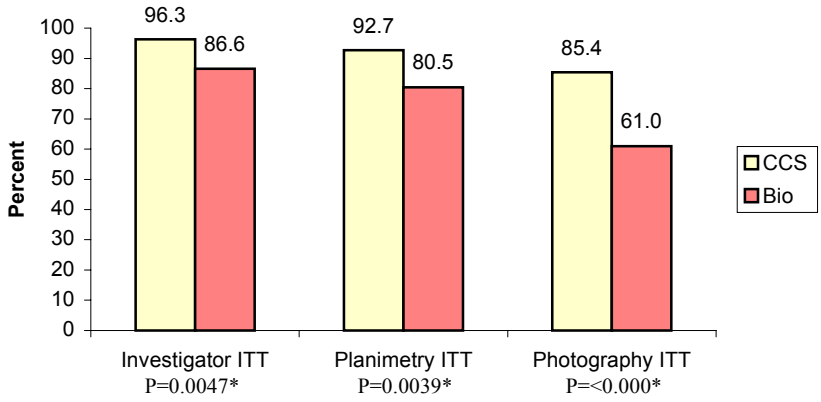
Figure 11.4.6: Photographic Assessment of Time to 100% Wound Closure ITT, Kaplan-Meier



Percentage of Donor Sites Healed by Day 32

Figures 11.4.7 and 11.4.8 depict the percentage of donor sites completely healed by day 32 for the ITT and PP populations, respectively, as assessed by investigator, planimetry, and photography. The percentage of CCS donor sites completely healed by day 32 was significantly higher ($p<0.05$) than those of Biobrane-L for all assessment methods and both populations.

Figure 11.4.7: Percentage of Sites Completely Healed by Day 32
ITT Population



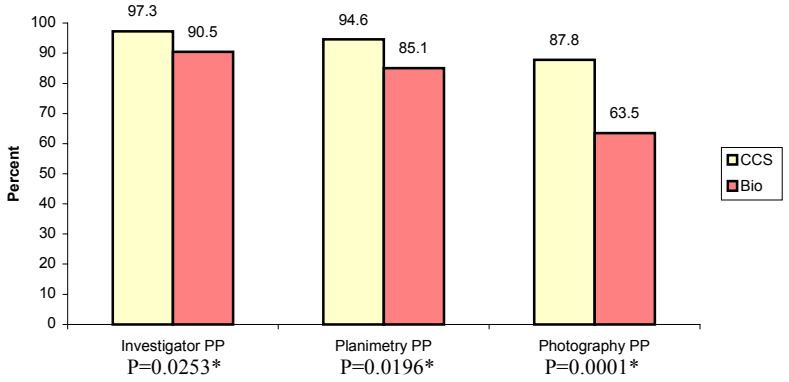
*McNemara's Test
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Table E.15

For the ITT population, CCS and Biobrane-L donor sites completely healed on day 32 were 96.3% and 86.6%, respectively, ($p=0.0047$) according to investigator assessment; 92.7% and 80.5%, respectively, ($p=0.0039$) according to planimetry; and 85.4% and 61.0%, respectively, ($p=<0.000$) by photography.

Similar results and significance levels were obtained with the PP population, as depicted in Figure 11.4.8.

Figure 11.4.8: Percentage of Sites Completely Healed by Day 32

Per Protocol Population



*McNemara's Test
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Tables E.16

Time to 95% and 98% Wound Closure

Kaplan-Meier estimates of median time to 95% and 98% wound closure, as assessed by planimetry, were also conducted. Figures 11.4.9 and 11.4.10, respectively, depict these median times for the ITT population.

Median times to 95% wound closure were 10 days for CCS and 13 Days for Biobrane-L; 98% wound closure was achieved in 11 days for CCS and 15 days for Biobrane-L sites.

Figure 11.4.9: Planimetric Assessment of Time to 95% Wound Closure ITT, Kaplan-Meier

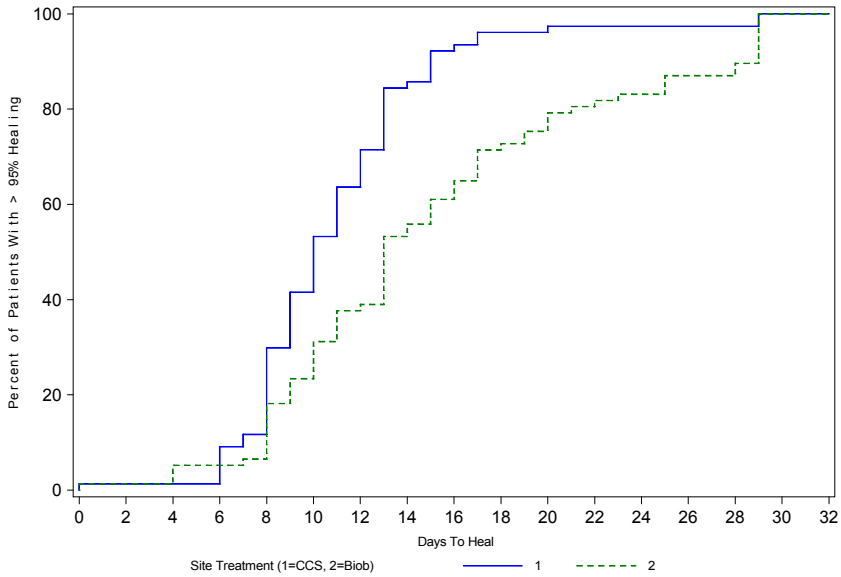


Figure 11.4.10: Planimetric Assessment of Time to 98% Wound Closure ITT, Kaplan-Meier